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Erlotinib and Gastrointestinal Ulcer

To the Editor:

Erlotinib is an orally available epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) and has been used as second- or third-line treatment for non-small cell lung cancer worldwide.[1] It is also approved for pancreatic cancer in combination with gemcitabine. Its toxicities are generally mild, with the major toxicities being skin rash, diarrhea, and liver dysfunction. Recently, however, Genentech and OSI Pharmaceuticals have issued important safety information, stating that patients receiving concomitant antiangiogenic agents, corticosteroids, nonsteroidal antiinflammatory drugs (NSAIDs), and/or taxane-based chemotherapy, or who have a history of peptic ulceration or diverticular disease are at greater risk for developing gastrointestinal perforation.[2]

Between March 2008 and March 2010, 103 patients with non-small cell lung cancer were treated with erlotinib in our hospital. All patients started erlotinib as a single agent at a dose of 150 mg/body/d. We reviewed these patients and identified five patients who developed gastrointestinal events during the treatment period: four patients with hemorrhagic gastrointestinal ulcer confirmed by gastrointestinal endoscopy and one patient with gastrointestinal perforation. Table 1 shows the characteristics of all 103 patients. The significance of the relationships between clinical factors and the onset of gastrointestinal events was evaluated using univariate analysis with Fisher's exact probability test. There were no significant associations between age, sex, performance status, history of peptic ulcer, and the concomitant use of steroids and anticoagulants and gastrointestinal events; however, only the use of NSAIDs was significantly associated: all five patients had received NSAIDs concomitantly with erlotinib in the gastrointestinal event (+) group, whereas 29 of 98 patients had received NSAIDs in the gastrointestinal event (−) group. In addition, four of five patients had not received either H_2-blockers or proton-pump inhibitors in the gastrointestinal event (+) group, whereas 18 of 29 patients had not received in the gastrointestinal event (−) group. Only one patient had received H_2-blocker in the gastrointestinal event (+) group; however, he had also received steroids and developed gastrointestinal perforation. The incidence rate of 4.9% (5 of 103) for gastrointestinal ulcer was fairly high, although there is no conclusive proof that all gastrointestinal events were caused with erlotinib; however, consid-

TABLE 1. Patient Characteristics

	Gastrointestinal Event (−) $n = 98$	Gastrointestinal Event (+) ($n = 5$)	p
Age (yr)			
<70	64	2	0.3472
≥70	34	3	
Sex			
Male	54	4	0.3831
Female	44	1	
PS			
0/1	72	2	0.1342
2/3/4	26	3	
Histology			
Ad	83	3	0.1898
Non-Ad	15	2	
Prior history of peptic ulcer			
Yes	7	0	>0.9999
No	91	5	
Use of NSAIDs			
Yes	24	5	0.0014*
No	74	0	
Use of steroids			
Yes	18	1	>0.9999
No	80	4	
Use of H_2-blockers			
Yes	22	1	>0.9999
No	76	4	
Use of PPIs			
Yes	5	0	>0.9999
No	93	5	
Use of anticoagulants			
Yes	4	1	0.2242
No	94	4	

PS, performance status; Ad, adenocarcinoma; NSAIDs, nonsteroidal antiinflammatory drugs; PPI, proton-pump inhibitor. *, statistically significant.

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ering the brief time to the events from the start of erlotinib (3, 3, 5, 21, and 58 days, respectively), it is highly probable.

Previous studies have shown that EGFR was highly expressed in the epithelium of the gastrointestinal tract, and severe developmental disorders of the gastrointestinal epithelium were induced in EGFR-knockout mice.[3,4] Taking into account these preclinical data, our results may not be so surprising.

In conclusion, erlotinib frequently induces gastrointestinal ulcer when patients are administered NSAIDs without antacids. Although antacids may weaken the effectiveness of erlotinib by reducing the blood concentration of erlotinib, on the basis of our experiences, patients should be given antacids to avoid gastrointestinal ulcer when erlotinib and NSAIDs are administered concomitantly.

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The Role of Surgery in the Management of Primary Thymic Mucosa-associated Lymphoid Tissue (MALT) Lymphoma

To the Editor:

We read with great interest the recent article in *Journal of Thoracic Oncology* by Shimizu et al.,[1] who proposed a diagnosis flow chart (Figure 3) for thymic mucosa-associated lymphoid tissue (MALT) lymphoma. The diagnosis flow chart is creative and valuable and presents a clear path of identifying thymic MALT lymphoma. We extend the topic by stressing the role of surgery in the management of this rare disease.

As a malignant disease, thymic MALT lymphoma must be diagnosed finally by histologic examinations, which are known as "golden standards." Given the extreme rarity of this disease, some typical characteristics, as described by Shimizu et al., may be important clues of thymic MALT lymphoma, but they are not yet "gold standard" in diagnosis of this disease. Thus, for exact histologic diagnosis, biopsy is necessary. But in small biopsy, such as percutaneous needle biopsy, it is sometimes difficult to differentiate thymic MALT lymphoma from thymoma because of similar histologic mixture of lymphoid cells and epithelial cells in small biopsies.[2] Then, surgery is usually unavoidable for enough tumor biopsy, as reported in most cases of the literature.

On the other hand, according to our experience and information from the literature, thymic MALT lymphoma seems to be a special lymphoma that develops mostly within the thymus and is often encapsulated by an intact membrane.[3] Local invasion or distal metastasis is barely reported for this disease. There should be no more difficulty to perform a surgery on thymic MALT lymphomas than on common thymomas. Therefore, we suggest that when thymic MALT lymphoma is highly suspected by some typical characteristics, surgery be reasonably recommended to manage the anterior mediastinal mass. Surgery should be performed not only as an approach of obtaining enough tissues for exact histologic diagnosis but also as a choice of effective treatment by removing the disease completely.

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In Response:

We thank Song and coworkers for their letter in response to our recent article on primary thymic mucosa-associated lymphoid tissue (MALT) lymphoma published in the *Journal of Thoracic Oncology*.[1] We recommended the diagnostic flow chart for a cystic thymic mass but did not address the role of surgery in the management of this rare disease.

Song and coworkers stressed the role of surgery in the management of thymic MALT lymphoma. They suggested that surgery should be performed not only as an approach of obtaining enough tissues for exact histologic diagnosis but also as a choice of effective treatment by removing the disease completely. We fully agree with their opinion. As has been reported in the literature, thymic MALT lymphoma is often encapsulated, and local invasion or distal metastasis has barely been reported.[1,2] If completely resected before it spreads, excellent outcome is expected. However, if the disease is left untreated and spreads beyond encapsulation, its management can be challenging.

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